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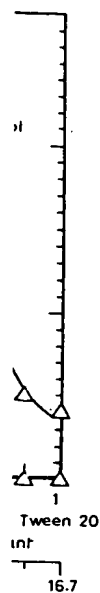
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SURFACTANT SYSTEMS

Their Chemistry, Pharmacy and Biology

D. Attwood and A.T. Florence



by addition of lauryl alcohol and 5% surfactant mixtures. Popophilic Span 20 at ratios and lines represent data for pure consisting of 8 parts mineral

the optimal ratio for water lauryl alcohol to the oil phase, addition of the polar oil has been published on the properties of the

of vaccines containing are first in 1968 and tested. The action of oil-in-water emulsions is well known but high viscosity which makes LB of 9.7 as the optimum. [238] found a value of 10. The surfactant Arlacel 80 polyoxyethylene (5)-sorbitol can be solubilized, when toxic and the amount which could

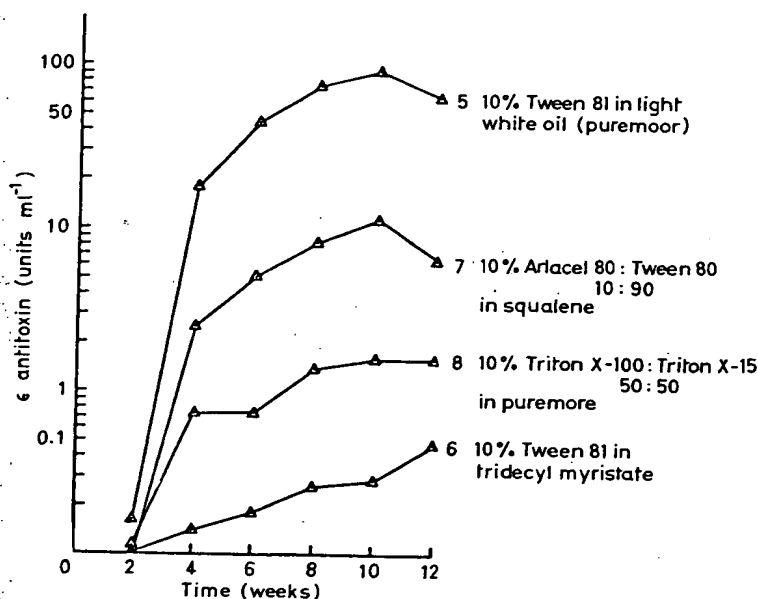


Figure 6.32 ϵ -Antitoxin titres in guinea-pig serum ($n = 6$) after 1 ml subcutaneous doses of vaccines 5–7 and a 0.2 ml dose of vaccine 8. From Coles *et al.* [238].

be solubilized. They also found that water was solubilized in paraffin oil and pure hydrocarbons, straight or branched, at lower concentrations in fatty alcohols and fatty acid esters and at extremely low concentrations in vegetable oils, pure triglycerides and fatty alcohol esters. This then limits non-aqueous solubilization for medicinal products. Vaccines in tridecyl myristate and squalene as well as mineral oil were examined and in one system (8) a Triton X-100/Triton X-15 mixture was used (unsuccessfully) as the solubilizer. ϵ -Antitoxin titres produced in rabbit serum on administration of four of these vaccine formulations are shown in Fig. 6.32. The tridecyl myristate system was unstable at 37°C with Arlacel and Tween mixtures but the solubilized systems are generally more stable than their emulsified counterparts, although not of course immune to destabilization in a biological environment. They are now more readily prepared than emulsions and have a lower viscosity.

6.4 Solubilization with block co-polymeric surfactants

So far in this chapter we have attempted to survey solubilization of pharmaceutical products by drug class. Here we diverge to discuss solubilization by a class of surfactant. For reasons of toxicity many ionic surfactants are excluded from serious contention as solubilizing agents for use in medicines. Not all non-

ionic surfactants are without blemish in this regard, as we will see in Chapter 9, and there must still be scope for the investigation of new surfactants which can be used with impunity.

An interesting class of non-ionic surface-active agents are polyoxyethylene-polyoxypropylene-polyoxyethylene block co-polymeric surfactants, sold under the trade name Pluronic and also known by their generic name as poloxamers [239]. Of the available block co-polymeric surfactants, the poloxamers have been most widely studied to date, yet there has been considerable confusion in the literature over the exact nature of their colloidal behaviour, in particular whether or not micelles are formed [240]. Recently, surface-tension measurements on a series of poloxamers in aqueous solution [241] and photon correlation spectroscopy [242] has helped to resolve some of these problems but as befits their structure their behaviour patterns tend to be complex. At low concentrations, approximating to those at which more conventional non-ionic detergents form micelles, the poloxamer monomers are thought to form monomolecular micelles by a change in configuration in solution. At higher concentrations these monomolecular micelles associate to form aggregates of varying size which have the ability to solubilize drugs [243] and to increase the stability of solubilized agents [244].

Table 6.27 lists approximate values of molecular weight and ethylene oxide and propylene oxide chain lengths for the poloxamers, and the designation of poloxamers and the commercial Pluronic surfactants.

Table 6.27 Approximate values of n , m and M for various polyoxyethylene-polyoxypropylene glycols (Pluronic or poloxamers)

Poloxamer designation	Pluronic* designation	Molecular weight of C_3H_6O -portion	m^\dagger	'Percent' C_2H_4O	Molecular weight of C_2H_4O -portion	n^\dagger	Total molecular weight, M
181	L61	1750	23	10	194	4	1944
182	L62	1750	23	20	438	10	2188
183	L63	1750	23	30	750	17	2500
184	L64	1750	23	40	1167	27	2917
185	P65	1750	23	50	1750	40	3500
188	F68	1750	23	80	7000	159	8750
231	L81	2250	30	10	250	6	2500
234	P84	2250	30	40	1500	34	3750
235	P85	2250	30	50	2250	51	4500
237	F87	2250	30	70	5250	119	7500
238	F88	2250	30	80	9000	205	11250
331	L101	3250	43	10	361	8	3611
333	P103	3250	43	30	1393	32	4643
335	P105	3250	43	50	3250	74	6500
338	F108	3250	43	80	13000	296	16250
101	L31	950	13	10	106	2	1056
401	L121	4000	53	10	444	10	4444

* F denotes 'solid', P denotes 'pasty' and L denotes 'liquid' consistencies at 25°C.

† Molecular weight of C_3H_6O - is 76 and of C_2H_4O - is 44.

Some relationships between the solubilities of the aqueous poloxamer polymer although the trend [243]. The solubility of p-nitroacetanilide is in line with the general trend shown by other compounds, but contradictory results have been reported to the π values of the compounds, expressed as the solubility against percentage of hydrophobic derivatives are thus negative. A linear relationship between the solubility of acetanilide, 4-fluoroacetanilide, 4-fluorobenzoate of the solubilizer (hydrophobe) is calculated, which is in some doubt that the micelle concentration with increasing HL to suspect that the relationship between the solubility of benzoate, for example, is greater than they do with parahydroxybenzoate. Pluronic than by p-

Table
acetan
against
cule a
Substit
H
4-OH
4-OMe
4-OEt
4-CHC
4-NO₂
4-F
4-Cl
4-Br
4-I

* From
† From

Some relationships between poloxamer structure and the solubilization of para-substituted acetanilides have been defined by Collett and Tobin [243]. The solubilities of the substituted acetanilides such as 4-hydroxyacetanilide, in aqueous poloxamer solutions increase with increasing oxyethylene content of the polymer although the more hydrophobic members of the series do not show this trend [243]. The results as expressed in Table 6.27 show that, for example, 4-nitroacetanilide is less soluble in the more hydrophilic poloxamers, and this is the general trend shown by the halogenated derivatives. These are apparently contradictory results. Some attempt was made to relate solubilization of the series to the π values of their functional groups. Thus in Table 6.28 we see solubilization expressed as the slope of the plot of mol drug solubilized mol^{-1} poloxamer against percentage ethylene oxide in the surfactant. Slope of the hydrophilic derivatives are thus positive and those of the more hydrophobic compounds, negative. A linear relationship is obtained for the solubilization of a hydrophobic acetanilide, 4-fluoroacetanilide and the propylene oxide-polyethylene oxide ratio of the solubilizer (Fig. 6.33a) but when the amount of drug solubilized by the hydrophobe is calculated it decreases as the hydrophobicity of the solubilize increases, which is contrary to expectation (Fig. 6.33b). Collett and Tobin suggest some hydrophobic barrier in the micelle which seems unlikely, but there is no doubt that the micellar properties are not as predicted [241]. Apparent critical micelle concentrations determined from surface tension measurements decrease with increasing HLB. The fact that this is contrary to expectation might lead one to suspect that these are not true CMCs but are the consequence of interaction between the solubilize and polymer. Methyl, ethyl, and propyl parahydroxybenzoate, for example, interact with poloxamer co-polymers to no greater extent than they do with polyoxyethylene glycol 6000 which does not micellize; butyl parahydroxybenzoate, on the other hand, is solubilized to a greater extent in this Pluronic than by polysorbate 80. The flexibility of the chains at the air-water

Table 6.28 The slopes for plots of mol *p*-substituted acetanilide solubilized mol^{-1} poloxamer (pH 1.0, 37° C) against percentage oxyethylene in the poloxamer molecule and the π value of the substituent (from [247])

Substituent	Slope, $K \times 10^2$	π^*
H	6.30	0
4-OH	15.0	-0.36
4-OMe	2.74	-0.133
4-OEt	0.31	0.367†
4-CHO	5.20	0.091
4-NO ₂	-0.32	0.499
4-F	-1.30	0.309
4-Cl	-0.78	0.714
4-Br	-1.03	1.130
4-I	-0.83	1.303

* From [245]

† From [246]

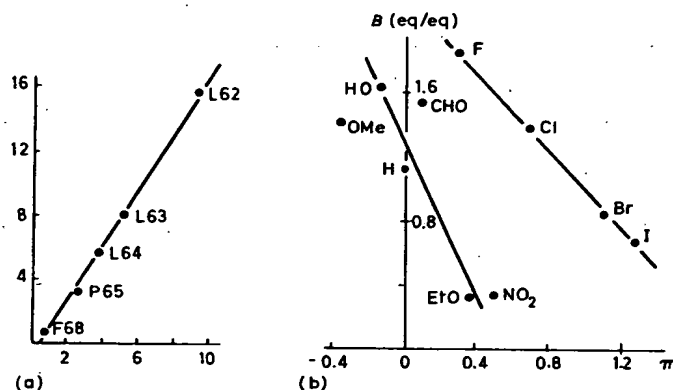


Figure 6.33(a) Solubilization of 4-fluoroacetanilide in aqueous solutions of poloxamers L62, L63, L64, P65 and F68 expressed as equivalents of drug per equivalent of ethylene oxide against the poloxamer mole ratio. Ordinate: $S/C_{EO} \times 10^2$ (equivalents of drug solubilized per equivalent of ethylene oxide). Abscissa: $C_R/C_{EO} \times 10^2$ (propylene oxide-ethylene oxide mol ratio). (b) The amount of *p*-substituted acetanilide solubilized (B) by the hydrophobe of poloxamer molecules as a function of the π value of the substituent group on the acetanilide molecule. From Collett and Tobin [247].

interface [241] suggests that the folding of the longer hydrophobic chains in bulk solution effectively decreases the exposed hydrophobic surface and this reduces the tendency to form polymolecular aggregates even though the monomer is calculated to be more hydrophobic through its HLB number. Another explanation of the trends may be that when the polyoxyethylene chains are short the molecules do not display sufficient amphipathy. Amphipathic properties increase with increase in the size of the hydrophile. Some evidence for this is that the addition of sodium chloride to a solution of poloxamer L64 causes a reduction in the measured mean radius of the aggregates in solution, suggesting that salting out of the hydrophile at both ends of the molecule converts it into a non-aggregating species, by making it more closely resemble a hydrocarbon chain [241].

Nuclear magnetic resonance has been used [248] to study the interaction of poloxamer F68 and phenol. Starting with low phenol concentrations, up to 2%, in a 10% aqueous poloxamer F68 solution, it was reported that the phenol was associated mainly with the polyoxypropylene chain. However, as the ratio of phenol to poloxamer increased, it appeared that the polyoxypropylene chain became saturated with phenol and relatively more phenol entered the polyoxyethylene chain.

A chlorhexidine gluconate-poloxamer 187 solution has been developed as an antiseptic skin cleansing formulation [249]. This contains 25% poloxamer 187, chosen to produce the greatest foaming capacity and also because the poloxamers as a class interfere with the activity of the chlorhexidine less than other non-

ionic surfactants tested. Choice of poloxamer re and its ability to solubi

Marked increases in achieved by dispersing carrier [251] (see Fig. 6. in the digoxin co-precip shown in Table 6.29 in v

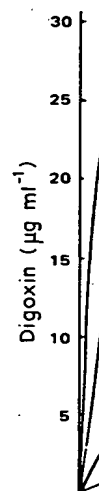


Figure 6.34 Dissolution of drug; Δ , 10 and 1% physio. From Neddy *et al.* [251].

Table 6.29 E solubility of

Test system
Water
Poloxamer 188
equivalent to
Poloxamer 188
equivalent to
Deoxycholic ac
equivalent to
Deoxycholic ac
equivalent to

From [251].

ionic surfactants tested. An alcohol-based mouthwash has also been described. Choice of poloxamer rested on lack of noxious taste (cf. some other non-ionics) and its ability to solubilize aromatic flavours [250].

Marked increases in the dissolution rate of digitoxin and digoxin has been achieved by dispersing the drugs in solid poloxamer 188 (Pluronic F68) as a carrier [251] (see Fig. 6.34). Poloxamer 188, in concentrations equivalent to that in the digoxin co-precipitates studied, increased the solubility of the digoxin as shown in Table 6.29 in which results are compared with the effects of deoxycholic

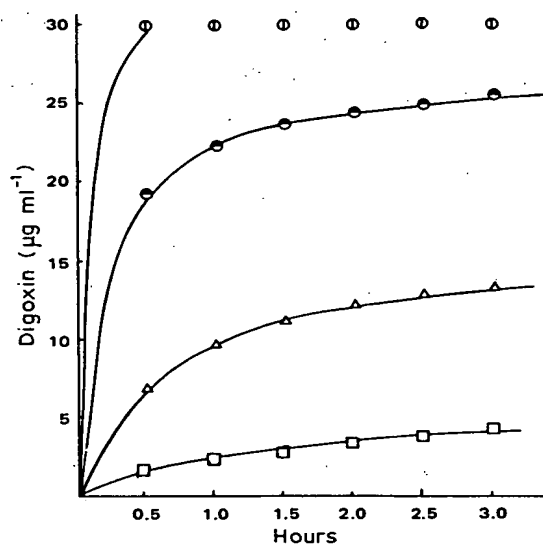


Figure 6.34 Dissolution of digoxin from poloxamer 188 test preparations. □, Untreated drug; Δ, 10 and 1% physical mixtures; ⊖, 10% co-precipitate; and ⊕, 1% co-precipitate. From Neddy *et al.* [251] with permission.

Table 6.29 Effect of poloxamer 188 and deoxycholic acid on the solubility of digoxin in water at 37° C

Test system	Solubility mg/100 ml
Water	3.47
Poloxamer 188 in concentration equivalent to 10% co-precipitate	4.77
Poloxamer 188 in concentration equivalent to 1% co-precipitate	5.38
Deoxycholic acid in concentration equivalent to 10% co-precipitate	4.62
Deoxycholic acid in concentration equivalent to 1% co-precipitate	4.25

From [251].

acid. Enhanced dissolution could be due to the presence of the drug in an amorphous state in the co-precipitate, to surface-tension lowering and to increase in the bulk solubility of the dry substance (see Chapter 7).

Poloxamers have also been incorporated into white petrolatum USP ointment bases in the presence of dimethylsulphoxide to modify the absorption of drugs presented in the base [252]. Percutaneous absorption of salicylic acid was increased significantly by poloxamers 231 and 182 and absorption of sodium salicylate by poloxamer 182.

Sheth and Parrott [244], in their study on the hydrolysis of esters, measured the solubility of benzocaine in a range of non-ionic surfactants including poloxamer 188. It was the least efficient, a Tetronic co-polymeric surfactant (Tetronic 908) having twice the solubilizing capacity. Tetronic is the proprietary name for the poloxamine series with the general structure,

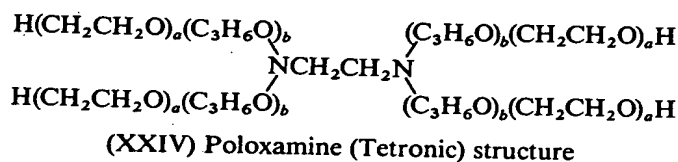


Table 6.30 Nomenclature of the meroxapol and poloxamine block co-polymeric surfactants

Hydrophobe molecular weight	Meroxapol series							
	31R1	31R2	—	31R4	—	—	—	—
3100	25R1	25R2	—	25R4	25R5	—	—	25R8
2500	17R1	17R2	—	17R4	—	—	—	17R8
1700	—	—	—	—	10R5	—	—	10R8
1000	—	—	—	—	—	—	—	—
	10	20	30	40	50	60	70	80
	% Ethylene oxide							

Hydrophobe molecular weight	Poloxamine series							
	1501	1502	—	1504	—	—	—	1508
6750	1301	1302	—	1304	—	—	1307	—
5750	1101	1102	—	1104	—	—	1107	—
4750	901	—	—	904	—	—	—	908
3750	701	702	—	704	—	—	707	—
2750	—	—	—	504	—	—	—	—
1750	—	—	—	304	—	—	—	—
750	—	—	—	—	—	—	—	—
	10	20	30	40	50	60	70	80
	% Ethylene oxide							

From Schmolka [239].

The nomenclature of 1,4-bis(oxazolinyl)ethylene-polyoxyethylene-polyoxamers is explained in Table 1. No generic name has the polymer chains with the

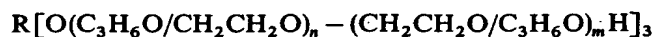


The solubilizing ability

6.5 Polymer-surfactant

Pharmaceutical formula hood of the presence of p of surfactant-polymer : surfactants to perform substance. Polymer-surf of polymers as viscosity between surfactants and polypropylene oxides [alcohol [260] have been polymer-surfactant con ergistic effect of the poly soluble dye [256, 257]. A media has also been re-surfactant increase with indeed it has proved pos: by the addition of surf complexes with opposit completely re-solubilized precipitation has been fo formed on the polymer c layer of surfactant was ac revealed that optimal is when the surfactant had terminal to the alkyl chai extent of the interaction being difficult to achieve As might be expected, polymers has a solubili surfactant alone. Fig. 6.34

The nomenclature of the poloxamers and the meroxapols (polyoxypropylene-polyoxyethylene-polyoxypropylene block co-polymers) 'reversed' poloxamers is explained in Table 6.30. Another class of block co-polymers which has no generic name has the name Pluradot (Wyandotte). These have three block co-polymer chains with the general formula,



$$\left(\frac{C_3H_6O}{C_2H_4O}\right) > 1 \quad \left(\frac{C_2H_4O}{C_3H_6O}\right) > 1$$

Pluradot structure
XXV

The solubilizing ability of these complex polymers has not been reported.

6.5 Polymer-surfactant interactions

Pharmaceutical formulations are rarely simple solutions. The increasing likelihood of the presence of polymers in formulations should alert us to the possibility of surfactant-polymer interactions which can influence the capacity of the surfactants to perform their function of increasing the solubility of drug substance. Polymer-surfactant interactions are of some interest in view of the use of polymers as viscosity modifiers and suspension stabilizers [253]. Interactions between surfactants and non-ionic polymers such as polyethylene oxides [254], polypropylene oxides [255], polyvinylpyrrolidone [256, 257] and polyvinyl-alcohol [260] have been studied [259]. An interesting property of some of these polymer-surfactant complexes, e.g. polyvinylpyrrolidone-NaLS, is the synergistic effect of the polymer on the capacity of the surfactant to solubilize oil-soluble dye [256, 257]. An instance of such synergism occurring in hydrocarbon media has also been reported [260]. Interactions between polymer and a given surfactant increase with the increasing hydrophobicity of the macromolecule; indeed it has proved possible to solubilize poorly soluble hydrophobic polymers by the addition of surfactant [261, 262]. Polyelectrolytes form precipitation complexes with oppositely charged surfactants which can in many cases be completely re-solubilized by the addition of excess surfactant [259]. Maximum precipitation has been found to occur when a single layer of adsorbed surfactant formed on the polymer chains; the resolubilized form appearing when a double layer of surfactant was achieved. Goddard and Hannan's detailed study [259] has revealed that optimal interactions between polymer and surfactant occurred when the surfactant had a long, straight hydrocarbon chain with the polar group terminal to the alkyl chain. Departure from this structural constraint reduces the extent of the interaction and also renders the resolubilization difficult, the latter being difficult to achieve if the charge density on the polymer is also high [259]. As might be expected, the complex formed between some surfactants and polymers has a solubilization capacity which is different from that of the surfactant alone. Fig. 6.35 shows the effect of PVP on the solubilization of Yellow

The
Condensed Chemical
Dictionary

EIGHTH EDITION

Revised by

GESSNER G. HAWLEY

*Formerly Executive Editor, Reinhold Publishing Corporation
Coeditor, Encyclopedia of Chemistry*



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PMP. Abbreviation for 1-phenyl-3-methyl-5-pyrazolone (q.v.).

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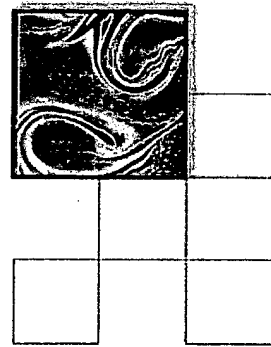
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PERFORMANCE CHEMICALS

PRODUCTS

Physical Chemistry



PLURONIC® surfactants, unlike conventional nonionic surfactants, do not micellize at a critical micelle concentration (CMC). Instead, aggregation occurs over a broad concentration range that we refer to as the ACR (aggregation concentration range). The limiting aggregation concentration (LAC) is the point at which the surfactant reaches saturation, which would correspond to the more conventional CMC. The ACRs and LACs for these surfactants occur at much higher orders of magnitude (for most of the products >1000 ppm) than for classical nonionic surfactants (commonly below 100 ppm) with a single hydrophile and a single hydrophobe, as shown below.

PLURONIC® Surfactants

Product	Aggregation Concentration	Limiting Aggregation
---------	---------------------------	----------------------

	Range (ppm)	Concentration (ppm)
L35	2,000-100,000	>100,000
P65	200-50,000	>50,000
P75	1,000-50,000	>50,000
P85	500-50,000	>50,000
P103	50-1,000	>1,000
P104	100-1,500	>1,500
P105	50-2,000	>2,000
F108	400-50,000	>50,000

Many of the unique performance benefits provided by PLURONIC surfactants and highlighted throughout this site can be explained on a molecular level by the unusual aggregation behavior observed with these products.

BASF Corporation has many years of expertise in research process development, production and application of EO/PO block copolymer surfactants.

These BASF surfactants range from flowable liquids of varying viscosities to pastes, pills and cast solids, with molecular weights from 1,000 to 30,000. All products are 100% active and all are easy to handle, physically stable and have an extremely low order of oral and dermal toxicity.

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